12. (Amended) The isolated and purified RT of claim 4 in which the amino acid sequences [Tyr-Xaa-Asp-Asp,] Ser-Xaa-Xaa$_1$-Xaa$_2$, Asn-Xaa-Xaa$_1$, Tyr-Xaa-Asp-Asp, and Xaa-Val-Thr-Gly are arranged in order starting from the amino terminal end of the RT.

REMARKS

Applicants submit this Amendment in response to the Office Action of September 4, 1996. This is a final rejection. There is no prior art rejection, only rejections under 37 U.S.C. §112, first paragraph as to enablement and second paragraph for indefiniteness. Applicants firmly believe that these issues can be resolved to mutual satisfaction.

The Examiner's Refusal to Consider the IDS

Preliminarily, Applicants respectfully disagree with the Examiner's refusal to consider the Information Disclosure Statement filed on June 5, 1996 on the ground stated by the Examiner: lack of certification or the necessary fee. The Information Disclosure Statement filed on June 5, 1996 complied with all requirements of 37 C.F.R. §1.97. Applicants submit as an attachment to this Amendment, a copy of the transmittal form which accompanied the Amendment and IDS filed on June 5, 1996. As clearly indicated on the transmittal form, a check for $220.00 to cover the filing fee for the IDS was enclosed. A copy of the cancelled check is also attached.

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Applicants submit that the information on the IDS, which was timely and properly submitted, must be considered as to the merits, as stated in 37 C.F.R. §1.97(c). Applicants' remarks below, addressed towards the issue of enablement, rely on Rice et al., "Diversity of Retron Elements in a Population of Rhizobia and Other Gram-Negative Bacteria", J. Bacteriol., 175(13):4250-4254 (1993), which article was submitted with the IDS.

Further, because the Rice et al. article was not considered, as stated by the Examiner on page 2 of the present Office Action, Applicants respectfully request the Examiner to withdraw the finality of the rejection as premature, as set forth in MPEP §§706.07(c) and (d).

Amendments to the Application

The specification has been amended to correct and to insert appropriate Sequence ID Nos. No new matter is added by the amendments to the specification. A revised Sequence Listing is attached hereto, including paper copy, computer readable copy, and statement under 37 C.F.R. §1.825.

The claims have been amended to insert Sequence ID Nos. for the individual sequences in claims 1, 2 and 4, and for clarification. The amendments are described in more detail below in the section dealing with rejections under 35 U.S.C. §112, second paragraph.

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Rejections under 35 U.S.C. §112, first paragraph

Lack of Enablement

The Examiner has rejected claims 1-7 and 9-13 under 35 U.S.C. §112, first paragraph, as not being enabled in scope beyond a reverse transcriptase (RT) from E. coli, which RT synthesizes msDNA.

Claim 13 is the broadest claim. It is found in the Amendment Under 37 C.F.R. §1.115 mailed June 5, 1996. The claim is drawn to an enzyme, a reverse transcriptase (RT), which is a bacterial reverse transcriptase. The claim calls for the enzyme to be isolated and purified. This RT is a specific one which is responsible for the production of an RNA-DNA hybrid molecule known as "msDNA" (multicopy, single-stranded DNA).

Claim 13 reads as follows:

> 13. An isolated and purified bacterial reverse transcriptase (RT) which synthesizes msDNA, and which is essential for the synthesis of msDNA in vivo.

The claim is not subject to any rejection but that of enablement.

The RNA-DNA hybrid molecule (msDNA) is known. It is known that the RT is responsible for the production of the msDNA molecules, indeed essential therefor. It is known to isolate and purify the enzyme. And, importantly, it is known how to test for the presence of msDNA which has been produced by the RT, in

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bacteria. These facts are all shown by the scientific literature, submitted below.

The inventors' discovery of the msDNA and the role of the RT in its synthesis is now textbook biotechnology. See Lewin, GENES IV, Oxford University Press 1990, pages 686-690, "Reverse Transcription Generates Branched RNA-DNA in Bacteria", attached hereto as Exhibit 1. The work of the inventors is recognized by Lewin on page 690 under "Discoveries":

> Branched RNA-DNA molecules were discovered by Furuichi, Inouye & Inouye (Cell 48, 55-62, 1987) and their synthesis by reverse transcriptase was characterized by Lampson, Inouye and Inouye (Cell 56, 709-717, 1989) and Lim & Maas (Cell 56, 891-904, 1989).

The work of the inventors was also recognized by the U.S. Patent Office in the grant of earlier patents, including on RTs from M. xanthus and E. coli, by U.S. Patents 5,434,070 and 5,320,958.

In the subject application, applicants have found that msDNA generated by an RT is more ubiquitous in bacteria than originally thought. See, for instance, Rice et al. (which includes Bert Lampson, one of the original and present inventors) filed with the IDS on June 5, 1996. Claim 13 is drawn to the reverse transcriptase from those bacteria which synthesizes the msDNA molecule.

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Applicants are of the view and submit that the evidence of what is known in the prior art, together with the teaching of the application, overwhelmingly shows that there is no question about "enablement" for one skilled in this technology.

For completeness, applicants answer the Examiner's statements in the Final Rejection.

As described more fully below, Applicants submit that the claims are fully enabled because:

1. the presence of msDNA in a bacteria conclusively proves that the bacteria contains reverse transcriptase, see Lim and Maas, Cell, Vol. 56:891-904 (1989) (note Summary, page 891, last sentence) attached hereto,

2. the RT is known to be encoded by a three-gene element known as a retron, which also codes for msr and msd portions of the msDNA,

3. tests for the presence of msDNA in a bacteria are known, see Rice et al., J. Bacteriol., Vol. 175(13):4250-4254 (1993), submitted with IDS of June 5, 1996, and

4. once the presence of the reverse transcriptase is ascertained, the reverse transcriptase can be isolated by procedures taught in the specification, see Example 3, pages 39-40, and disclosed in the prior art, see Lampson, et al., PNAS, Vol. 40:1-24 (1991) (note page 13, first paragraph), cited in the specification on page 40, line 17, and attached hereto.

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5. Therefore, what is required to practice the invention as claimed is to simply test for msDNA, which shows the presence of the RT, and then isolate the RT as taught in the specification.

Accordingly, Applicants submit that the invention as claimed is fully enabled, in accordance with 35 U.S.C. §112, first paragraph.

Applicants herebelow respond in detail to the statements of the Examiner in the Office Action.

A. The Claims Are Fully Enabled to the Scope Claimed

In the Amendment filed June 5, 1996, Applicants submitted that the Examiner had misread the specification and the claims. In the present Office Action, on page 3, the Examiner has provided his understanding of the invention, as a "demonstration" that:

> (a) the Examiner has not misread or misinterpreted the claimed invention or the specification, and (b) that applicants' instant claims are not enabled by the specification.

The Examiner states that the specification teaches two screening tests by which one skilled in the art can readily determine whether a bacteria contains a retron for synthesizing msDNA. The Examiner continues:

> Once this retron is determined to exist, it must be identified and screened. Then any

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resultant RT must be produced and identified. The result is one skilled in the art is left to do the experimenting, screening, and further experimenting on their own, finally determining if such an RT exists, and then attempting to isolate such an RT after this.

The Examiner overlooks the fact that no screening for a retron is needed, or is performed. As taught in the specification, and as explained in the previous Amendment, the only screening that is needed to practice the invention, in the scope claimed, is to screen bacteria by one of two routine screening tests for the presence of msDNA, not for the retron, and thus for RT, which tests are taught in the specification.

Following this screening test, the existence of RT in the bacteria is definitively established because if the bacteria contains msDNA, it must contain RT. The retron, which contains genes for msr, msd, and RT, is not identified or screened, as stated by the Examiner. In order to isolate the RT which has been determined to exist, one skilled in the art has only to follow the teaching of the present specification in Example 3, pages 39-40. Alternatively, as taught in the specification on page 40, lines 16-18, the RT may be isolated by the method taught in Lampson et al., "msDNA of Bacteria", Progress in Nucleic Acid Res. and Mol. Biol., vol. 40, pages 1 et seq.

i.e. You need the retron!

The above sequence of steps was what was reported in Rice et al., the publication provided with the IDS of June 6, 1996, which was not considered by the Examiner. Thus, Rice et al.

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provides a showing that one skilled in the art may readily follow the teaching of the specification to screen and identify bacteria which produce msDNA, and which therefore, contain RT.

On page 4250, first column, second paragraph, last sentence, Rice et al. disclose that:

> it is now well established that the retron-encoded RT is responsible for the synthesis of msDNA. (citing Lim and Maas, Cell, vol. 56:891-904 (1989), and Lampson et al., Cell, vol. 56:701-707 (1989), both of which are attached hereto).

On page 4250, first column, fourth paragraph, first sentence, Rice et al. disclose that:

> Retron elements were discovered by detecting the presence of msDNA by the RT extension method.

Rice et al. screened for the presence of msDNA, and thus for RT, at least 20 isolates from each of Proteus mirabilis, Klebsiella pneumoniae, Salmonella spp., rhizobial species, and enterococcal species. See page 4250, first column, fourth paragraph, lines 6-9. Of these isolates, msDNA was found in 4 of 23 P. mirabilis (17%), 1 of 21 K. pneumoniae (5%), 4 of 70 Salmonella (6%), and 10 of 63 rhizobial isolates (16%). Over 10% of the isolates tested were shown to contain msDNA. See page 4250, second column, second full paragraph, lines 1-3, and page 4251, second column, first full paragraph, lines 6-7.

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The RT, which is established to exist by the presence of the msDNA, is isolated from the bacteria based on its activity, irrespective of the sequence of the RT. See Example 3 of the specification.

Thus, because only routine experimentation is required to practice the invention as claimed, Applicants submit that the claims are fully enabled, and request the Examiner to withdraw the rejection of the claims on this ground.

B. The Claims Are Fully Enabled Irrespective of the Conserved Amino Acid Sequences Called for in Dependent Claims

The Examiner states, on pages 3 to 5 of the Office Action, that the presence of conserved amino acid sequences, as called for in dependent claims, does not aid one skilled in the art to identify and isolate the claimed RT.

Applicants respectfully submit, however, that the presence of the conserved amino acid sequences is not necessary for the identification of bacteria which produce an RT and for isolation of the RT, which isolation is performed irrespective of sequence of the RT. It is clear from what has been stated above, that the amino acid sequence of the RT has nothing to do with its isolation.

The function of these dependent claims is to allow one skilled in the art who wishes to use a particular RT, to identify such an RT having a particular sequence. Claim 13 is enabled. The dependent claims are not required for enablement.

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Rather than calling for features to aid in isolating the claimed RT, the dependent claims calling for the conserved amino acid sequences add additional features which further define the RT once it is isolated by the presence of "signature" sequences.

C. Only Routine Experimentation Is Required To Practice the Invention

The Examiner states, on page 4, bottom paragraph, that, because of the large amount of bacteria that can be screened according to the claimed method of the invention, the required experimentation is undue. Applicants respectfully submit, however, that, applying the criteria of MPEP §2164 et seq., the experimentation required is not undue and the claims are fully enabled.

As stated in MPEP §2164.01,

> Whether undue experimentation is needed is not based upon a single factor, but rather a conclusion reached by weighing many factors. Many of these factors have been summarized in In re Wands, 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988) . . .

Applying the following In re Wands criteria to the present application, it is clear that only routine, and not undue, experimentation is required to practice the invention.

1. The quantity of experimentation required is not excessive, because a routine screening test is taught, which

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screening test detected the presence of msDNA in bacteria in about 10% or more of isolates tested.

2. The specification directly guides one skilled in the art as to what experimentation is necessary, that is, a candidate bacterial isolate is screened for the presence of msDNA, which indicates the presence of RT.

3. The specification provides a variety of examples of bacteria that produce msDNA and RT. Myxococcus xanthus - page 14, line 8, Stigmatella aurantiaca - page 14, line 11, Escherichia coli - page 17, line 20, Proteus, Klebsiella, Salmonella, Rhizobium, Bradyrhizobium, and Nannocystis - page 32, lines 16-18, and page 39, lines 4-13. Detailed working examples are supplied for M. xanthus, E. coli, and rhizobial isolates - page 33, last paragraph, page 35, lines 9-19, and page 38, lines 10-24.

4. The nature of the invention is a protein which is required for the production of an msDNA structure, which structure is identifiable by means of a routine screening test.

5. Methods for screening bacteria for the presence of msDNA, such as the RT extension method taught in the specification and performed by Rice et al., are known.

6. One skilled in the art is sophisticated, having at least a Masters degree, or perhaps a Ph.D., in microbiology or molecular biology.

7. The art is predictable, as it is known for certain that, if a bacteria makes msDNA, it must produce RT. Very simply,

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there is a direct and necessary demonstrated correlation: A bacteria which synthesizes msDNA has made RT. One does not exist without the other.

8. The claims encompass an RT made from a bacteria.

The accuracy of the analysis of the above factors is evident from the Rice et al. article, which discloses the identification of msDNA, and therefore RT, in several genera of bacteria, which bacteria had not been known previously to produce msDNA.

Applicants submit that, in accordance with the standards for enablement as set forth in the MPEP and in In re Wands, any experimentation required to practice the present invention, as claimed, is routine and is not undue, and that the claims are fully enabled.

Accordingly, for the reasons set forth above, Applicants respectfully submit that the rejection of the claims under 35 U.S.C. §112, first paragraph, for lack of enablement as to scope, is overcome, and request the Examiner to reconsider and to withdraw the rejection of the claims on this ground.

Rejections under 35 U.S.C. §112, second paragraph

A. Claims 1-4 have been amended to delete the term "has" and replace by the term "contains".

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B. Claim 3 was amended in the Amendment of June 5, 1996 to delete the term "conserved". The sequence in claim 3 does not require a Sequence ID No. because it is three amino acids long.

C. Claims 1, 2, and 4 have been amended to supply Sequence ID Nos. for each of the claimed sequences.

D. Claim 12 has been amended to change the order of the sequences. Moreover, because each of the claimed sequences has its own Sequence ID No., and are not related to any single Sequence ID No., the order of the sequences is immaterial.

E. Claim 7 has been amended to replace the term "has" by the open term "contains", and to delete the term "conserved".

F. Claim 5 has been amended to remove any indefiniteness. Applicants submit that reference to Figure 14 is appropriate according to MPEP §2173.05(s), which states that reference to a figure is permitted:

> where there is no practical way to define the invention in words and where it is more concise to incorporate by reference rather than duplicating a drawing or table into the claim.

Applicants submit that the amendments to the claims overcome the rejections under 35 U.S.C. §112, second paragraph, and respectfully request the Examiner to withdraw the rejection of the claims on this ground.

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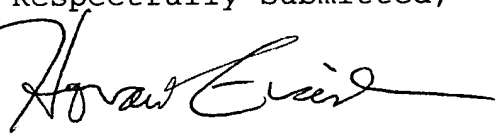
Rejections under 35 U.S.C. §103

Applicants cofile and attach hereto appropriate terminal disclaimers relating to U.S. Patent Nos. 5,320,958 and 5,434,070.

Conclusion

Applicants request the Examiner to withdraw the finality of rejection for failure to consider prior art which had been properly submitted in an IDS prior to the mailing of the present Office Action. Applicants submit that the claims, as amended herein, are in condition for allowance, and request an early notice to that effect.

Respectfully submitted,



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Margaret Termini

12/4/96 Margaret Termini
DATE SIGNATURE

Attachments: Transmittal form for Amendment and IDS of June 5, 1996
Cancelled check
Terminal Disclaimers (2)
Sequence Listing (paper and computer readable copies) with Statement under 37 C.F.R. §1.825
Lim and Maas, Cell, vol. 56:891-904 (1989)
Lampson et al., Cell, vol. 56:701-707 (1989)
Lampson, et al., PNAS, vol. 40:1-24 (1991)
Exhibit 1, Lewin, GENES IV, Oxford University Press 1990, pp. 686-690

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